

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

## PCT

To:

see form PCT/ISA/220

### WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/US2005/017158

International filing date (day/month/year)  
18.05.2005

Priority date (day/month/year)  
18.05.2004

International Patent Classification (IPC) or both national classification and IPC  
INV. A61P25/24 A61K31/365 A61K31/192 A61K31/196 A61K31/045 A61K31/05 A61K31/4164 A61K31/4172

Applicant  
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**1. This opinion contains indications relating to the following items:**

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

**2. FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

**3. For further details, see notes to Form PCT/ISA/220.**

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this opinion

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material:

- ☐ a sequence listing
- ☐ table(s) related to the sequence listing

b. format of material:

- ☐ on paper
- ☐ in electronic form

c. time of filing/furnishing:

- ☐ contained in the international application as filed.
- ☐ filed together with the international application in electronic form.
- ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 1-2, 8, 11, 23-25 (partially); 3-7, 9-10, 12-22, 26-46 (completely)

because:

- ☒ the said international application, or the said claims Nos. 1-2, 8, 11, 23-25 (with regard to industrial applicability) relate to the following subject matter which does not require an international search (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-2, 8, 23-25 (partially); 3-7, 9-10, 12-22, 26-46 (completely)
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
  - ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
  - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
  - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13 *ter*.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See Supplemental Box for further details

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**Box No. IV Lack of unity of invention**

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1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
  - ☐ paid additional fees under protest and, where applicable, the protest fee
  - ☐ paid additional fees under protest but the applicable protest fee was not paid
  - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
  - ☒ not complied with for the following reasons:  
    **see separate sheet**
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
  - ☒ the parts relating to claims Nos. 1-2, 8, 23-25 (partially); 11 (completely)

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**Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	-
	No: Claims	1-2, 8, 11, 23-25
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-2, 8, 11, 23-25
Industrial applicability (IA)	Yes: Claims	-
	No: Claims	1-2, 8, 11, 23-25

2. Citations and explanations

**see separate sheet**

**Re Item III.**

III.1 No opinion will be given in respect of subject-matter which is not covered by the search report (Rule 66.1 (e) PCT).

III.2 The claims of the first invention relate to subject-matter considered by this authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item IV.**

The separate inventions/groups of inventions are:

1

Claims 1-2, 8, 23-25 (partially); 11 (completely)

A method according to claims 1 or 23 comprising administering a composition comprising a carbonic anhydrase activator and a pharmaceutically acceptable carrier to said subject, wherein the activator is phenylalanine

2

Claims 1-3, 8, 23-25 (partially); 12-17 (completely)

A method according to claims 1 or 23 comprising administering a composition comprising a carbonic anhydrase activator and a pharmaceutically acceptable carrier to said subject, wherein the activator is a derivatic phenylalanine amino acid as outlined in said claims

3

Claims 1, 4-5, 8, 23-25 (partially); 9 (completely)

A method according to claims 1 or 23 comprising administering a composition comprising a carbonic anhydrase activator and a pharmaceutically acceptable carrier to said subject, wherein the activator is histidine, also substituted as outlined in said claims

4

Claims 1-5, 8, 23, 25 (partially); 10, 18, 19-22, 26, 27 (completely)

A method according to claims 1 or 23 comprising administering a composition comprising a carbonic anhydrase activator and a pharmaceutically acceptable carrier to said subject, wherein the activator is an aromatic amine according to the application

5

Claims 1, 8, 28 (partially); 6 (completely)

A method comprising the steps of identifying a subject with a depressive disorder and administering a composition comprising a carbonic anhydrase activator and a pharmaceutically acceptable carrier to said subject, wherein the activator is a compound of Structure II according to the application

6

Claims 1, 8, 28 (partially); 7 (completely)

A method comprising the steps of identifying a subject with a depressive disorder and administering a composition comprising a carbonic anhydrase activator and a pharmaceutically acceptable carrier to said subject, wherein the activator is Structure III according to the application

7

Claims 29-38 (completely)

A method comprising the steps of identifying a subject with a depressive disorder and administering a composition comprising a protein C kinase activator including fibroblast growth factors and a pharmaceutically acceptable carrier to said subject according to claim 29 or 34

8

Claims 39-46 (completely)

A method of screening according to claim 39

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The problems to be solved by the present application are

- (1) the treatment of depressive disorders,
- (2) obtaining agents for treating depressive disorders.

The proposed solutions are

- (1) to use compounds which improve learning and memory, which are carbonic anhydrase (CA) activators or protein C kinase activators, including fibroblast growth factors
- (2) the screening methods of claim 39, ie. a swimming test with a test subject indicative for anti-depressive activity.

According to Article 3 (4) (iii) PCT, an international application shall comply with the "prescribed requirement of unity of invention". This means, as explained in Rule 13.1 PCT, that the application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

Anti-depressant activity as a general concept represents the technical feature which may, a priori, unify the problems/solutions 1) - 2) mentioned above.

WO9832464 describes a tyrosine combination for the treatment of depression (see claim 1). The applicant has singled out tyrosine as a compound of the present application (see claim 17).

Similarly, Männistö P T et al., 1995, VOL - 274, p. 229-233 (see abstract), disclose positive effects of L-dihydroxyphenylalanine (singled out by the applicant as a compound of the present application) in animal models of depression.

Kravitz et al., Journal of the American Osteopathic Association, 1984, Vol. 84, Nr.1 SUPPL., P. 119-123 disclose dietary supplements of phenylalanine, a preferred compound of the present application, and other amino acid precursors of brain neuroamines in the treatment of depressive disorders.

Consequently, the general concept of this application is known in the prior art and, as a result,

this common concept cannot fulfil the role of a general inventive concept in the sense of Rule 13.1 PCT.

Concerning the "method of identifying a subject with a depressive disorder" mentioned in the claims, said claims (and the application as a whole) do not indicate any specific technical features relating to said method of identification. Therefore, said identification/diagnosis can only be carried out along the lines of a standard medical dictionary, eg. D3 (page 1531, column 2, paragraph 2 - page 1532, column 2). Consulting a standard textbook for identifying a certain disease in patients, however, clearly represents common knowledge employed by any medical doctor treating said disease (here: depression). Consequently, said feature cannot confer novelty to the present common concept over the cited documents.

In so far as the objections raised above could be overcome, the present common concept would still lack an inventive step over said documents, as the subject-matter of the present claims in as far as it could be novel appears to be obvious over said documents.

In addition, Casini et al., BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, VOL - 13, P. 2765-2768 disclose (see abstract) that the efficacy of certain SSRI inhibitors in treating depression may - at least - partly be due to their effect as carbonic anhydrase activators. The document strongly suggests that potent CA activators are useful for the treatment of major depression (see conclusions, page 2767, column 2, paragraph 2). Phenylalanine, a preferred compound of the present application, is singled out as the most potent activator of the CA isozyme hCA II, thus also strongly suggesting its usefulness for the treatment of depression.

Independent of the above objections, the applicant is reminded that the use of a substance for the manufacture of a medicament for the treatment of a specific disease can only be patented if this use is new and inventive. Consequently, a common concept (Rule 13.1 PCT) relating to the use of substances acting via newly-specified mechanisms of action for the treatment of specific diseases can only be considered a common inventive concept under Rule 13.1 PCT if all of the claimed variants are new and inventive. In any case, patenting a use in form of a different or newly-specified mechanism of action is impossible. In fact, the discovery of such mechanisms of action ("carbonic anhydrase activators") does not represent an invention as the resulting technical effect remains the same (treatment of depressive



disorders). In the present case, the discovery of alternative mechanisms of action does not add a new or improved technical effect to well-known medical uses; the technical effect is not modified by the discovery of an alternative mechanism of action (also see Rule 39.1 PCT).

The problem to be solved by the first group of inventions is the treatment of depressive disorders.

The solution presented is to use compounds which improve learning and memory, which are

- (I) carbonic anhydrase (CA) activators
- (II) proteins C kinase activators; including fibroblast growth factors.

The common concept of the first group of inventions could be formulated as the use of compounds which improve learning and memory, which are carbonic anhydrase activators or proteins C kinase activators, incl. fibroblast growth factors for the treatment of depressive disorders.

Again, WO9832464 describes a tyrosine combination for the treatment of depression (see claim 1). The applicant has singled out tyrosine as a compound of the present application (see claim 17).

Similarly, Männistö P T et al., 1995, VOL - 274, P. 229-233 (see abstract), disclose positive effects of L-dihydroxyphenylalanine (singled out by the applicant as a compound of the present application) in animal models of depression.

Kravitz et al., Journal of the American Osteopathic Association, 1984, Vol. 84, Nr.1 SUPPL., P. 119-123 disclose dietary supplements of phenylalanine, a preferred compound of the present application, and other amino acid precursors of brain neuroamines in the treatment of depressive disorders.

Consequently, the general concept of this group of inventions is known in the prior art and, as a result, this common concept cannot fulfil the role of a general inventive concept in the sense of Rule 13.1 PCT.

In so far as the objections raised above could be overcome, the present common concept would still lack an inventive step over said documents, as the subject-matter of the present claims in as far as it could be novel appears to be obvious over said documents.

In addition, Casini et al., BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, VOL - 13, P. 2765-2768 disclose (see abstract) that the efficacy of certain SSRI inhibitors in treating depression may - at least - partly be due to their effect as carbonic anhydrase activators. The document strongly suggests that potent CA activators are useful for the treatment of major depression (see conclusions, page 2767, column 2, paragraph 2). Phenylalanine, a preferred compound of the present application, is singled out as the most potent activator of the CA isozyme hCA II, thus also strongly suggesting its usefulness for the treatment of depression.

The problem to be solved by the first sub-group of inventions is the treatment of depressive disorders.

The solution presented is to use compounds which improve learning and memory, which are carbonic anhydrase (CA) activators, either of

- (i) Structure I
- (ii) Structure II
- (iii) Structure III

as outlined in claim 1.

The common concept of the first sub-group of inventions could be formulated as the use of compounds which improve learning and memory which are carbonic anhydrase activators for the treatment of depressive disorders.

Again, WO9832464 describes a tyrosine combination for the treatment of depression (see claim 1). The applicant has singled out tyrosine (falling under structure I) as a compound of the present application (see claim 17).

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Similarly, Männistö P T et al., 1995, VOL - 274, P. 229-233 (see abstract), disclose positive effects of L-dihydroxyphenylalanine (singled out by the applicant as a compound of the present application and falling under structure I) in animal models of depression.

Kravitz et al., Journal of the American Osteopathic Association, 1984, Vol. 84, Nr.1 SUPPL., P. 119-123 disclose dietary supplements of phenylalanine, a preferred compound of the present application and falling under structure I, and other amino acid precursors of brain neuroamines in the treatment of depressive disorders.

Consequently, the present general concept is known in the prior art and, as a result, this common concept cannot fulfil the role of a general inventive concept in the sense of Rule 13.1 PCT.

In so far as the objections raised above could be overcome, the present common concept would still lack an inventive step over said documents, as the subject-matter of the present claims in as far as it could be novel appears to be obvious over said documents.

In addition, Casini et al., BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, VOL - 13, P. 2765-2768 disclose (see abstract) that the efficacy of certain SSRI inhibitors in treating depression may - at least - partly be due to their effect as carbonic anhydrase activators. The document strongly suggests that potent CA activators are useful for the treatment of major depression (see conclusions, page 2767, column 2, paragraph 2). Phenylalanine (falling under structure I), a preferred compound of the present application, is singled out as the most potent activator of the CA isozyme hCA II, thus also strongly suggesting its usefulness for the treatment of depression.

The problem to be solved by the first sub-sub-group of inventions is the treatment of depressive disorders.

The solution presented is to use compounds which improve learning and memory, which are carbonic anhydrase (CA) activators of Structure I as outlined in claim 1, in particular

(A) aromatic amino acids and

(B) aromatic amines.

The present common concept could be formulated as the use of compounds which improve learning and memory which are carbonic anhydrase activators of Structure I according to the application for the treatment of depressive disorders.

Again, WO9832464 describes a tyrosine combination for the treatment of depression (see claim 1). The applicant has singled out tyrosine (falling under structure I) as a compound of the present application (see claim 17).

Similarly, Männistö P T et al., 1995, VOL - 274, P. 229-233 (see abstract), disclose positive effects of L-dihydroxyphenylalanine (singled out by the applicant as a compound of the present application and falling under structure I) in animal models of depression.

Kravitz et al., Journal of the American Osteopathic Association, 1984, Vol. 84, Nr.1 SUPPL., P. 119-123 disclose dietary supplements of phenylalanine, a preferred aromatic amino acid of the present application and falling under structure I, and other amino acid precursors of brain neuroamines in the treatment of depressive disorders.

Consequently, the present general concept is known in the prior art and, as a result, this common concept cannot fulfil the role of a general inventive concept in the sense of Rule 13.1 PCT.

In so far as the objections raised above could be overcome, the present common concept would still lack an inventive step over said documents, as the subject-matter of the present claims in as far as it could be novel appears to be obvious over said documents.

In addition, Casini et al., BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, VOL - 13, P. 2765-2768 disclose (see abstract) that the efficacy of certain SSRI inhibitors in treating depression may - at least - partly be due to their effect as carbonic anhydrase activators. The document strongly suggests that potent CA activators are useful for the treatment of major depression (see conclusions, page 2767, column 2, paragraph 2). Phenylalanine (falling under structure I), a preferred compound of the present application, is singled out as the most potent activator of the CA isozyme hCA II, thus also strongly

suggesting its usefulness for the treatment of depression.

The problem to be solved by the first sub-sub-sub-group of inventions is the treatment of depressive disorders.

The solution presented is to use aromatic amino acids which improve learning and memory, which are carbonic anhydrase (CA) activators of Structure I as outlined in claim 1, in particular

- (1) phenylalanine and its derivatic amino acids
- (2) histidine

The present common concept could be formulated as the use of aromatic amino acids which improve learning and memory which are carbonic anhydrase activators of Structure I according to the application for the treatment of depressive disorders.

Again, WO9832464 describes a tyrosine combination for the treatment of depression (see claim 1). The applicant has singled out tyrosine (an aromatic amino acid falling under structure I) as a compound of the present application (see claim 17).

Similarly, Männistö P T et al., 1995, VOL - 274, P. 229-233 (see abstract), disclose positive effects of the aromatic amino acid L-dihydroxyphenylalanine (singled out by the applicant as a compound of the present application and falling under structure I) in animal models of depression.

Kravitz et al., Journal of the American Osteopathic Association, 1984, Vol. 84, Nr.1 SUPPL., P. 119-123 disclose dietary supplements of phenylalanine, a preferred compound of the present application and falling under structure I, and other amino acid precursors of brain neuroamines in the treatment of depressive disorders.

Consequently, the present general concept is known in the prior art and, as a result, this common concept cannot fulfil the role of a general inventive concept in the sense of Rule 13.1 PCT.

In so far as the objections raised above could be overcome, the present common concept would still lack an inventive step over said documents, as the subject-matter of the present claims in as far as it could be novel appears to be obvious over said documents.

In addition, Casini et al., BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, VOL - 13, P. 2765-2768 disclose (see abstract) that the efficacy of certain SSRI inhibitors in treating depression may - at least - partly be due to their effect as carbonic anhydrase activators. The document strongly suggests that potent CA activators are useful for the treatment of major depression (see conclusions, page 2767, column 2, paragraph 2). Phenylalanine (falling under structure I), a preferred compound of the present application, is singled out as the most potent activator of the CA isozyme hCA II, thus also strongly suggesting its usefulness for the treatment of depression.

The problem to be solved by the first sub-sub-sub-sub-group of inventions is the treatment of depressive disorders.

The solution presented is to use

- (aa) phenylalanine and
- (bb) derivatic phenylalanine amino acids

which improve learning and memory, which are carbonic anhydrase (CA) activators of Structure I as outlined in claim 1.

The present common concept could be formulated as the use of phenylalanine and its derivatic amino acids which improve learning and memory which are carbonic anhydrase activators of Structure I according to the application for the treatment of depressive disorders.

Again, WO9832464 describes a tyrosine combination for the treatment of depression (see claim 1). The applicant has singled out tyrosine (an aromatic amino acid falling under structure I) as a compound of the present application (see claim 17).

Similarly, Männistö P T et al., 1995, VOL - 274, P. 229-233 (see abstract), disclose positive

effects of the aromatic amino acid L-dihydroxyphenylalanine (singled out by the applicant as a compound of the present application and falling under structure I) in animal models of depression.

Kravitz et al., Journal of the American Osteopathic Association, 1984, Vol. 84, Nr.1 SUPPL., P. 119-123 disclose dietary supplements of phenylalanine, a preferred compound of the present application and falling under structure I, and other amino acid precursors of brain neuroamines in the treatment of depressive disorders.

Consequently, the present general concept is known in the prior art and, as a result, this common concept cannot fulfil the role of a general inventive concept in the sense of Rule 13.1 PCT.

In so far as the objections raised above could be overcome, the present common concept would still lack an inventive step over said documents, as the subject-matter of the present claims in as far as it could be novel appears to be obvious over said documents.

In addition, Casini et al., BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, VOL - 13, P. 2765-2768 disclose (see abstract) that the efficacy of certain SSRI inhibitors in treating depression may - at least - partly be due to their effect as carbonic anhydrase activators. The document strongly suggests that potent CA activators are useful for the treatment of major depression (see conclusions, page 2767, column 2, paragraph 2). Phenylalanine (falling under structure I), a preferred compound of the present application, is singled out as the most potent activator of the CA isozyme hCA II, thus also strongly suggesting its usefulness for the treatment of depression.

In the present application, no further technical feature in the sense of Rule 13.2 PCT can be distinguished that could be regarded as a "special technical feature" involved in the technical relationship among the different inventions.

Hence, the present application lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as the different subjects as listed above.

Each of the inventions is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

**As additional search fees have not been paid yet, the present Written Opinion refers to the first invention, only.**

**Re Item V.**

The applicant's attention is drawn to the fact that the present opinion expressed as to novelty, inventive step and industrial applicability refers only to matter for which an international search report has been drawn up, i.e. for the first invention. No opinion will be given in respect of subject-matter which is not covered by the search report.

**V.1 Article 33(4) PCT**

The subject-matter of the claims of the first invention involves compositions or substances in a method of treatment/diagnosis practised on the human/animal body. For the assessment of these claims on the question whether they are industrially applicable, no unitary criteria exist in the PCT Contracting states. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise the subject-matter of claims related to the use of a compound in medical treatment/diagnosis practised on the human/animal body as industrially applicable.

**V.2 Reference is made to the following documents:**

D1 : KRAVITZ H M ET AL: "Dietary supplements of phenylalanine and other amino acid precursors of brain neuroamines in the treatment of depressive disorders" JOURNAL OF THE AMERICAN OSTEOPATHIC ASSOCIATION 1984 UNITED STATES, vol. 84, no. 1 SUPPL., 1984, pages 119-123, XP002392551

D2 : CASINI A ET AL: "CARBONIC ANHYDRASE ACTIVATORS, THE SELECTIVE



SEROTONIN REUPTAKE INHIBITORS FLUOXETINE, SERTRALINE AND CITALOPRAM ARE STRONG ACTIVATORS OF ISOZYMES I AND II" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 13, no. 16, 18 August 2003 (2003-08-18), pages 2765-2768, XP008065595 ISSN: 0960-894X cited in the application

D3 : BEERS ET AL.: "Merck Manual" 1999, MERCK , WHITEHOUSE STATION, N.J. , XP002398044

**V.3 INDEPENDENT CLAIMS 1 AND 23 AND DEPENDENT CLAIMS 2, 8, 11, 24, 25**

The subject-matter of the first invention is a method comprising the steps of identifying a subject with a depressive disorder and administering a composition comprising a carbonic anhydrase activator and a pharmaceutically acceptable carrier to said subject, wherein the activator is phenylalanine.

V.3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of said claims is not new in the sense of Article 33(2) PCT.

Document D1 discloses (abstract) dietary supplements of phenylalanine and other amino acid precursors of brain neuroamines in the treatment of depressive disorders.

Concerning the "method of identifying a subject with a depressive disorder" mentioned in the claims, said claims (and the application as a whole) do not indicate any specific technical features relating to said method of identification. Therefore, said identification can only be carried out along the lines of a standard medical dictionary, eg. D3 (page 1531, column 2, paragraph 2 - page 1532, column 2). Consulting a standard textbook for identifying a certain disease in patients, however, clearly represents common knowledge employed by any medical doctor treating said disease (here: depression). Consequently, said feature cannot confer novelty to the present invention over the cited documents.

V.3.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of said claims is not inventive in the sense of Article 33(3) PCT.

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In so far as the objections of lack of novelty raised above could be overcome, the application would still lack an inventive step over D1, as the subject-matter of the present claims in as far as it could be novel appears to be obvious over said documents.

In addition, document D2 disclose (see abstract) that the efficacy of certain SSRI inhibitors in treating depression may - at least - partly be due to their effect as carbonic anhydrase activators. The document strongly suggests that potent CA activators are useful for the treatment of major depression (see conclusions, page 2767, column 2, paragraph 2). Phenylalanine is singled out as the most potent activator of the CA isozyme hCA II, thus also strongly suggesting its usefulness for the treatment of depression.

# PATENT COOPERATION TREATY

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### WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing  
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**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/US2005/017158

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International Patent Classification (IPC) or both national classification and IPC  
INV. A61P25/24 A61K31/365 A61K31/192 A61K31/196 A61K31/045 A61K31/05 A61K31/4164 A61K31/4172

Applicant  
BLANCHETTE ROCKEFELLER NEUROSCIENCES INSTITUTE

#### 1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

#### 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

#### 3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Date of completion of  
this opinion

see form  
PCT/ISA/210

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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material:

- ☐ a sequence listing
- ☐ table(s) related to the sequence listing

b. format of material:

- ☐ on paper
- ☐ in electronic form

c. time of filing/furnishing:

- ☐ contained in the international application as filed.
- ☐ filed together with the international application in electronic form.
- ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 1-2, 8, 11, 23-25 (partially); 3-7, 9-10, 12-22, 26-46 (completely)

because:

- ☒ the said international application, or the said claims Nos. 1-2, 8, 11, 23-25 (with regard to industrial applicability) relate to the following subject matter which does not require an international search (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-2, 8, 23-25 (partially); 3-7, 9-10, 12-22, 26-46 (completely)
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
  - ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
  - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
  - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details

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**Box No. IV Lack of unity of invention**

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1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
  - ☐ paid additional fees under protest and, where applicable, the protest fee
  - ☐ paid additional fees under protest but the applicable protest fee was not paid
  - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
  - ☒ not complied with for the following reasons:  
**see separate sheet**
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
  - ☒ the parts relating to claims Nos. 1-2, 8, 23-25 (partially); 11 (completely)

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**Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	-
	No: Claims	1-2, 8, 11, 23-25
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-2, 8, 11, 23-25
Industrial applicability (IA)	Yes: Claims	-
	No: Claims	1-2, 8, 11, 23-25

2. Citations and explanations

**see separate sheet**

**Re Item III.**

III.1 No opinion will be given in respect of subject-matter which is not covered by the search report (Rule 66.1 (e) PCT).

III.2 The claims of the first invention relate to subject-matter considered by this authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item IV.**

The separate inventions/groups of inventions are:

1

Claims 1-2, 8, 23-25 (partially); 11 (completely)

A method according to claims 1 or 23 comprising administering a composition comprising a carbonic anhydrase activator and a pharmaceutically acceptable carrier to said subject, wherein the activator is phenylalanine

2

Claims 1-3, 8, 23-25 (partially); 12-17 (completely)

A method according to claims 1 or 23 comprising administering a composition comprising a carbonic anhydrase activator and a pharmaceutically acceptable carrier to said subject, wherein the activator is a derivatic phenylalanine amino acid as outlined in said claims

3

Claims 1, 4-5, 8, 23-25 (partially); 9 (completely)

A method according to claims 1 or 23 comprising administering a composition comprising a carbonic anhydrase activator and a pharmaceutically acceptable carrier to said subject, wherein the activator is histidine, also substituted as outlined in said claims

4

Claims 1-5, 8, 23, 25 (partially); 10, 18, 19-22, 26, 27 (completely)

A method according to claims 1 or 23 comprising administering a composition comprising a carbonic anhydrase activator and a pharmaceutically acceptable carrier to said subject, wherein the activator is an aromatic amine according to the application

5

Claims 1, 8, 28 (partially); 6 (completely)

A method comprising the steps of identifying a subject with a depressive disorder and administering a composition comprising a carbonic anhydrase activator and a pharmaceutically acceptable carrier to said subject, wherein the activator is a compound of Structure II according to the application

6

Claims 1, 8, 28 (partially); 7 (completely)

A method comprising the steps of identifying a subject with a depressive disorder and administering a composition comprising a carbonic anhydrase activator and a pharmaceutically acceptable carrier to said subject, wherein the activator is Structure III according to the application

7

Claims 29-38 (completely)

A method comprising the steps of identifying a subject with a depressive disorder and administering a composition comprising a protein C kinase activator including fibroblast growth factors and a pharmaceutically acceptable carrier to said subject according to claim 29 or 34

8

Claims 39-46 (completely)

A method of screening according to claim 39

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:



The problems to be solved by the present application are

- (1) the treatment of depressive disorders,
- (2) obtaining agents for treating depressive disorders.

The proposed solutions are

- (1) to use compounds which improve learning and memory, which are carbonic anhydrase (CA) activators or protein C kinase activators, including fibroblast growth factors
- (2) the screening methods of claim 39, ie. a swimming test with a test subject indicative for anti-depressive activity.

According to Article 3 (4) (iii) PCT, an international application shall comply with the "prescribed requirement of unity of invention". This means, as explained in Rule 13.1 PCT, that the application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

Anti-depressant activity as a general concept represents the technical feature which may, a priori, unify the problems/solutions 1) - 2) mentioned above.

WO9832464 describes a tyrosine combination for the treatment of depression (see claim 1). The applicant has singled out tyrosine as a compound of the present application (see claim 17).

Similarly, Männistö P T et al., 1995, VOL - 274, p. 229-233 (see abstract), disclose positive effects of L-dihydroxyphenylalanine (singled out by the applicant as a compound of the present application) in animal models of depression.

Kravitz et al., Journal of the American Osteopathic Association, 1984, Vol. 84, Nr.1 SUPPL., P. 119-123 disclose dietary supplements of phenylalanine, a preferred compound of the present application, and other amino acid precursors of brain neuroamines in the treatment of depressive disorders.

Consequently, the general concept of this application is known in the prior art and, as a result,

this common concept cannot fulfil the role of a general inventive concept in the sense of Rule 13.1 PCT.

Concerning the "method of identifying a subject with a depressive disorder" mentioned in the claims, said claims (and the application as a whole) do not indicate any specific technical features relating to said method of identification. Therefore, said identification/diagnosis can only be carried out along the lines of a standard medical dictionary, eg. D3 (page 1531, column 2, paragraph 2 - page 1532, column 2). Consulting a standard textbook for identifying a certain disease in patients, however, clearly represents common knowledge employed by any medical doctor treating said disease (here: depression). Consequently, said feature cannot confer novelty to the present common concept over the cited documents.

In so far as the objections raised above could be overcome, the present common concept would still lack an inventive step over said documents, as the subject-matter of the present claims in as far as it could be novel appears to be obvious over said documents.

In addition, Casini et al., BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, VOL - 13, P. 2765-2768 disclose (see abstract) that the efficacy of certain SSRI inhibitors in treating depression may - at least - partly be due to their effect as carbonic anhydrase activators. The document strongly suggests that potent CA activators are useful for the treatment of major depression (see conclusions, page 2767, column 2, paragraph 2). Phenylalanine, a preferred compound of the present application, is singled out as the most potent activator of the CA isozyme hCA II, thus also strongly suggesting its usefulness for the treatment of depression.

Independent of the above objections, the applicant is reminded that the use of a substance for the manufacture of a medicament for the treatment of a specific disease can only be patented if this use is new and inventive. Consequently, a common concept (Rule 13.1 PCT) relating to the use of substances acting via newly-specified mechanisms of action for the treatment of specific diseases can only be considered a common inventive concept under Rule 13.1 PCT if all of the claimed variants are new and inventive. In any case, patenting a use in form of a different or newly-specified mechanism of action is impossible. In fact, the discovery of such mechanisms of action ("carbonic anhydrase activators") does not represent an invention as the resulting technical effect remains the same (treatment of depressive

disorders). In the present case, the discovery of alternative mechanisms of action does not add a new or improved technical effect to well-known medical uses; the technical effect is not modified by the discovery of an alternative mechanism of action (also see Rule 39.1 PCT).

The problem to be solved by the first group of inventions is the treatment of depressive disorders.

The solution presented is to use compounds which improve learning and memory, which are

- (I) carbonic anhydrase (CA) activators
- (II) proteins C kinase activators, including fibroblast growth factors.

The common concept of the first group of inventions could be formulated as the use of compounds which improve learning and memory, which are carbonic anhydrase activators or proteins C kinase activators, incl. fibroblast growth factors for the treatment of depressive disorders.

Again, WO9832464 describes a tyrosine combination for the treatment of depression (see claim 1). The applicant has singled out tyrosine as a compound of the present application (see claim 17).

Similarly, Männistö P T et al., 1995, VOL - 274, P. 229-233 (see abstract), disclose positive effects of L-dihydroxyphenylalanine (singled out by the applicant as a compound of the present application) in animal models of depression.

Kravitz et al., Journal of the American Osteopathic Association, 1984, Vol. 84, Nr.1 SUPPL., P. 119-123 disclose dietary supplements of phenylalanine, a preferred compound of the present application, and other amino acid precursors of brain neuroamines in the treatment of depressive disorders.

Consequently, the general concept of this group of inventions is known in the prior art and, as a result, this common concept cannot fulfil the role of a general inventive concept in the sense of Rule 13.1 PCT.

In so far as the objections raised above could be overcome, the present common concept would still lack an inventive step over said documents, as the subject-matter of the present claims in as far as it could be novel appears to be obvious over said documents.

In addition, Casini et al., BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, VOL - 13, P. 2765-2768 disclose (see abstract) that the efficacy of certain SSRI inhibitors in treating depression may - at least - partly be due to their effect as carbonic anhydrase activators. The document strongly suggests that potent CA activators are useful for the treatment of major depression (see conclusions, page 2767, column 2, paragraph 2). Phenylalanine, a preferred compound of the present application, is singled out as the most potent activator of the CA isozyme hCA II, thus also strongly suggesting its usefulness for the treatment of depression.

The problem to be solved by the first sub-group of inventions is the treatment of depressive disorders.

The solution presented is to use compounds which improve learning and memory, which are carbonic anhydrase (CA) activators, either of

- (i) Structure I
- (ii) Structure II
- (iii) Structure III

as outlined in claim 1.

The common concept of the first sub-group of inventions could be formulated as the use of compounds which improve learning and memory which are carbonic anhydrase activators for the treatment of depressive disorders.

Again, WO9832464 describes a tyrosine combination for the treatment of depression (see claim 1). The applicant has singled out tyrosine (falling under structure I) as a compound of the present application (see claim 17).

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Similarly, Männistö P T et al., 1995, VOL - 274, P. 229-233 (see abstract), disclose positive effects of L-dihydroxyphenylalanine (singled out by the applicant as a compound of the present application and falling under structure I) in animal models of depression.

Kravitz et al., Journal of the American Osteopathic Association, 1984, Vol. 84, Nr.1 SUPPL., P. 119-123 disclose dietary supplements of phenylalanine, a preferred compound of the present application and falling under structure I, and other amino acid precursors of brain neuroamines in the treatment of depressive disorders.

Consequently, the present general concept is known in the prior art and, as a result, this common concept cannot fulfil the role of a general inventive concept in the sense of Rule 13.1 PCT.

In so far as the objections raised above could be overcome, the present common concept would still lack an inventive step over said documents, as the subject-matter of the present claims in as far as it could be novel appears to be obvious over said documents.

In addition, Casini et al., BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, VOL - 13, P. 2765-2768 disclose (see abstract) that the efficacy of certain SSRI inhibitors in treating depression may - at least - partly be due to their effect as carbonic anhydrase activators. The document strongly suggests that potent CA activators are useful for the treatment of major depression (see conclusions, page 2767, column 2, paragraph 2). Phenylalanine (falling under structure I), a preferred compound of the present application, is singled out as the most potent activator of the CA isozyme hCA II, thus also strongly suggesting its usefulness for the treatment of depression.

The problem to be solved by the first sub-sub-group of inventions is the treatment of depressive disorders.

The solution presented is to use compounds which improve learning and memory, which are carbonic anhydrase (CA) activators of Structure I as outlined in claim 1, in particular

(A) aromatic amino acids and

(B) aromatic amines.

The present common concept could be formulated as the use of compounds which improve learning and memory which are carbonic anhydrase activators of Structure I according to the application for the treatment of depressive disorders.

Again, WO9832464 describes a tyrosine combination for the treatment of depression (see claim 1). The applicant has singled out tyrosine (falling under structure I) as a compound of the present application (see claim 17).

Similarly, Männistö P T et al., 1995, VOL - 274, P. 229-233 (see abstract), disclose positive effects of L-dihydroxyphenylalanine (singled out by the applicant as a compound of the present application and falling under structure I) in animal models of depression.

Kravitz et al., Journal of the American Osteopathic Association, 1984, Vol. 84, Nr.1 SUPPL., P. 119-123 disclose dietary supplements of phenylalanine, a preferred aromatic amino acid of the present application and falling under structure I, and other amino acid precursors of brain neuroamines in the treatment of depressive disorders.

Consequently, the present general concept is known in the prior art and, as a result, this common concept cannot fulfil the role of a general inventive concept in the sense of Rule 13.1 PCT.

In so far as the objections raised above could be overcome, the present common concept would still lack an inventive step over said documents, as the subject-matter of the present claims in as far as it could be novel appears to be obvious over said documents.

In addition, Casini et al., BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, VOL - 13, P. 2765-2768 disclose (see abstract) that the efficacy of certain SSRI inhibitors in treating depression may - at least - partly be due to their effect as carbonic anhydrase activators. The document strongly suggests that potent CA activators are useful for the treatment of major depression (see conclusions, page 2767, column 2, paragraph 2). Phenylalanine (falling under structure I), a preferred compound of the present application, is singled out as the most potent activator of the CA isozyme hCA II, thus also strongly

suggesting its usefulness for the treatment of depression.

The problem to be solved by the first sub-sub-sub-group of inventions is the treatment of depressive disorders.

The solution presented is to use aromatic amino acids which improve learning and memory, which are carbonic anhydrase (CA) activators of Structure I as outlined in claim 1, in particular

- (1) phenylalanine and its derivatic amino acids
- (2) histidine

The present common concept could be formulated as the use of aromatic amino acids which improve learning and memory which are carbonic anhydrase activators of Structure I according to the application for the treatment of depressive disorders.

Again, WO9832464 describes a tyrosine combination for the treatment of depression (see claim 1). The applicant has singled out tyrosine (an aromatic amino acid falling under structure I) as a compound of the present application (see claim 17).

Similarly, Männistö P T et al., 1995, VOL - 274, P. 229-233 (see abstract), disclose positive effects of the aromatic amino acid L-dihydroxyphenylalanine (singled out by the applicant as a compound of the present application and falling under structure I) in animal models of depression.

Kravitz et al., Journal of the American Osteopathic Association, 1984, Vol. 84, Nr.1 SUPPL., P. 119-123 disclose dietary supplements of phenylalanine, a preferred compound of the present application and falling under structure I, and other amino acid precursors of brain neuroamines in the treatment of depressive disorders.

Consequently, the present general concept is known in the prior art and, as a result, this common concept cannot fulfil the role of a general inventive concept in the sense of Rule 13.1 PCT.

In so far as the objections raised above could be overcome, the present common concept would still lack an inventive step over said documents, as the subject-matter of the present claims in as far as it could be novel appears to be obvious over said documents.

In addition, Casini et al., BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, VOL - 13, P. 2765-2768 disclose (see abstract) that the efficacy of certain SSRI inhibitors in treating depression may - at least - partly be due to their effect as carbonic anhydrase activators. The document strongly suggests that potent CA activators are useful for the treatment of major depression (see conclusions, page 2767, column 2, paragraph 2). Phenylalanine (falling under structure I), a preferred compound of the present application, is singled out as the most potent activator of the CA isozyme hCA II, thus also strongly suggesting its usefulness for the treatment of depression.

The problem to be solved by the first sub-sub-sub-sub-group of inventions is the treatment of depressive disorders.

The solution presented is to use

- (aa) phenylalanine and
- (bb) derivatic phenylalanine amino acids

which improve learning and memory, which are carbonic anhydrase (CA) activators of Structure I as outlined in claim 1.

The present common concept could be formulated as the use of phenylalanine and its derivatic amino acids which improve learning and memory which are carbonic anhydrase activators of Structure I according to the application for the treatment of depressive disorders.

Again, WO9832464 describes a tyrosine combination for the treatment of depression (see claim 1). The applicant has singled out tyrosine (an aromatic amino acid falling under structure I) as a compound of the present application (see claim 17).

Similarly, Männistö P T et al., 1995, VOL - 274, P. 229-233 (see abstract), disclose positive



effects of the aromatic amino acid L-dihydroxyphenylalanine (singled out by the applicant as a compound of the present application and falling under structure I) in animal models of depression.

Kravitz et al., Journal of the American Osteopathic Association, 1984, Vol. 84, Nr.1 SUPPL., P. 119-123 disclose dietary supplements of phenylalanine, a preferred compound of the present application and falling under structure I, and other amino acid precursors of brain neuroamines in the treatment of depressive disorders.

Consequently, the present general concept is known in the prior art and, as a result, this common concept cannot fulfil the role of a general inventive concept in the sense of Rule 13.1 PCT.

In so far as the objections raised above could be overcome, the present common concept would still lack an inventive step over said documents, as the subject-matter of the present claims in as far as it could be novel appears to be obvious over said documents.

In addition, Casini et al., BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, VOL - 13, P. 2765-2768 disclose (see abstract) that the efficacy of certain SSRI inhibitors in treating depression may - at least - partly be due to their effect as carbonic anhydrase activators. The document strongly suggests that potent CA activators are useful for the treatment of major depression (see conclusions, page 2767, column 2, paragraph 2). Phenylalanine (falling under structure I), a preferred compound of the present application, is singled out as the most potent activator of the CA isozyme hCA II, thus also strongly suggesting its usefulness for the treatment of depression.

In the present application, no further technical feature in the sense of Rule 13.2 PCT can be distinguished that could be regarded as a "special technical feature" involved in the technical relationship among the different inventions.

Hence, the present application lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as the different subjects as listed above.

Each of the inventions is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

**As additional search fees have not been paid yet, the present Written Opinion refers to the first invention, only.**

**Re Item V.**

The applicant's attention is drawn to the fact that the present opinion expressed as to novelty, inventive step and industrial applicability refers only to matter for which an international search report has been drawn up, i.e. for the first invention. No opinion will be given in respect of subject-matter which is not covered by the search report.

**V.1 Article 33(4) PCT**

The subject-matter of the claims of the first invention involves compositions or substances in a method of treatment/diagnosis practised on the human/animal body. For the assessment of these claims on the question whether they are industrially applicable, no unitary criteria exist in the PCT Contracting states. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise the subject-matter of claims related to the use of a compound in medical treatment/diagnosis practised on the human/animal body as industrially applicable.

**V.2 Reference is made to the following documents:**

**D1 : KRAVITZ H M ET AL: "Dietary supplements of phenylalanine and other amino acid precursors of brain neuroamines in the treatment of depressive disorders" JOURNAL OF THE AMERICAN OSTEOPATHIC ASSOCIATION 1984 UNITED STATES, vol. 84, no. 1 SUPPL., 1984, pages 119-123, XP002392551**

**D2 : CASINI A ET AL: "CARBONIC ANHYDRASE ACTIVATORS, THE SELECTIVE**

SEROTONIN REUPTAKE INHIBITORS FLUOXETINE, SERTRALINE AND CITALOPRAM ARE STRONG ACTIVATORS OF ISOZYMES I AND II" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 13, no. 16, 18 August 2003 (2003-08-18), pages 2765-2768, XP008065595 ISSN: 0960-894X cited in the application

D3 : BEERS ET AL.: "Merck Manual" 1999, MERCK , WHITEHOUSE STATION, N.J. , XP002398044

**V.3 INDEPENDENT CLAIMS 1 AND 23 AND DEPENDENT CLAIMS 2, 8, 11, 24, 25**

The subject-matter of the first invention is a method comprising the steps of identifying a subject with a depressive disorder and administering a composition comprising a carbonic anhydrase activator and a pharmaceutically acceptable carrier to said subject, wherein the activator is phenylalanine.

V.3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of said claims is not new in the sense of Article 33(2) PCT.

Document D1 discloses (abstract) dietary supplements of phenylalanine and other amino acid precursors of brain neuroamines in the treatment of depressive disorders.

Concerning the "method of identifying a subject with a depressive disorder" mentioned in the claims, said claims (and the application as a whole) do not indicate any specific technical features relating to said method of identification. Therefore, said identification can only be carried out along the lines of a standard medical dictionary, eg. D3 (page 1531, column 2, paragraph 2 - page 1532, column 2). Consulting a standard textbook for identifying a certain disease in patients, however, clearly represents common knowledge employed by any medical doctor treating said disease (here: depression). Consequently, said feature cannot confer novelty to the present invention over the cited documents.

V.3.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of said claims is not inventive in the sense of Article 33(3) PCT.

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In so far as the objections of lack of novelty raised above could be overcome, the application would still lack an inventive step over D1, as the subject-matter of the present claims in as far as it could be novel appears to be obvious over said documents.

In addition, document D2 disclose (see abstract) that the efficacy of certain SSRI inhibitors in treating depression may - at least - partly be due to their effect as carbonic anhydrase activators. The document strongly suggests that potent CA activators are useful for the treatment of major depression (see conclusions, page 2767, column 2, paragraph 2). Phenylalanine is singled out as the most potent activator of the CA isozyme hCA II, thus also strongly suggesting its usefulness for the treatment of depression.